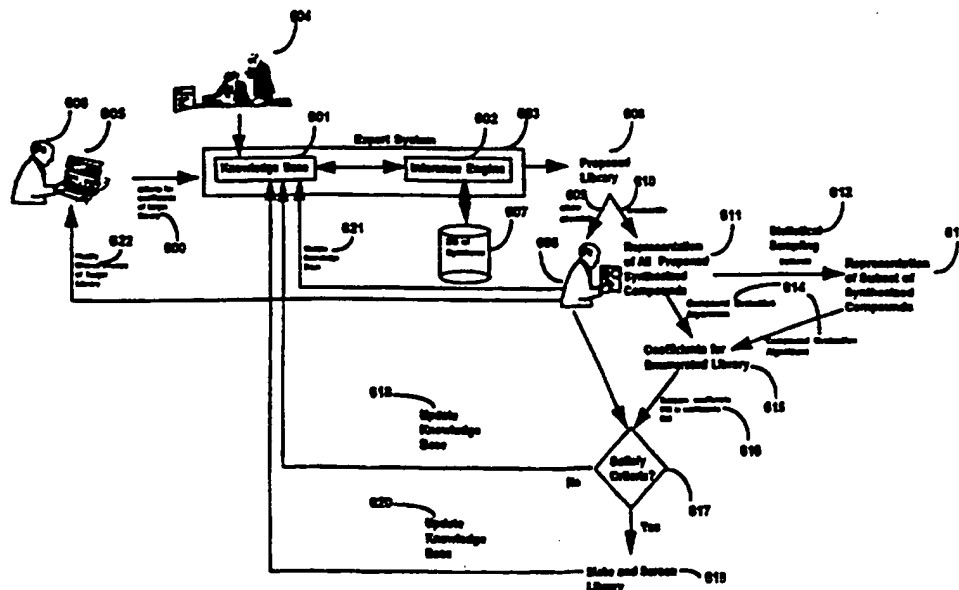




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**(54) Title: TECHNIQUE FOR REPRESENTING COMBINATORIAL CHEMISTRY LIBRARIES RESULTING FROM SELECTIVE COMBINATION OF SYNTHONS**



**(57) Abstract**

A method and apparatus is provided for the generation and representation of chemical libraries (608). More particularly, a computer implemented method and apparatus is provided for the generation and representation of combinatorial chemistry libraries (608).

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TECHNIQUE FOR REPRESENTING COMBINATORIAL  
CHEMISTRY LIBRARIES RESULTING FROM  
SELECTIVE COMBINATION OF SYNTHEONS

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TECHNICAL FIELD

This invention relates to combinatorial chemistry, and more particularly, to an improved technique for representing libraries resulting from combinatorial chemistry.

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BACKGROUND OF THE INVENTION

This invention relates to a system and method useful for the generation and representation of chemical libraries and, more particularly, to a computer-implemented system and method useful for the generation and representation of combinatorial chemistry libraries.

Combinatorial chemistry allows scientists to generate large numbers of unique molecules with a small number of chemical reactions. Rather than using the traditional approach of synthesizing novel compounds one at a time, compounds are synthesized by performing chemical reactions in stages, and reacting all of the molecules formed in stage n-1 with each reactant in stage n. An example of this process is shown in Figure 1. While, for purposes of this example, it is assumed that R1-R9 of Figure 1 represent single reactants which are used to perform

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single reactions, those skilled in the art will appreciate that any or all of R1-Rn can represent multiple reactions with which different types of chemistry or chemical sequences can be performed.

5                   In stage 1 of the example of Figure 1, molecules A and B are reacted with reactant R1. Similarly, molecules C and D are reacted with reactant R2, and molecules E and F are reacted with reactant R3 (although only one of each type of molecule is shown in Figure 1, many of each type are used  
10                   in the first stage and, consequently, many of each type are formed in subsequent stages). Molecules A-F are the "starting molecules," and the molecules formed after each stage are represented in Figure 1 by the starting molecule followed by the sequence of reactants separated by colons.

15                   In stage 2, all of the molecules formed in stage 1 are reacted with reactants R4, R5 and R6, and in stage 3, all of the molecules formed in stage 2 are reacted with reactants R7, R8 and R9. As is shown in Figure 1, this process generates 54 diverse molecules after stage 3, having  
20                   started with only six molecules and having performed only nine reactions. The diverse library of molecules thus formed may be used to screen for biological activity against a therapeutic target or for any other desirable property.

A general formula for the maximum number of unique molecules which can be formed using a combinatorial process is

$$\prod_{j=2}^N R_j \left( \sum_{n=1}^K m_n \right)$$

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where N is the number of stages, R is the number of reactants at stage j, K is the total number of reactants in the first stage, and m is the number of molecules reacted with reactant n. This formula represents the maximum number of unique molecules formed because it is possible for different reaction steps to generate the same compounds.

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The following references are related to combinatorial chemistry, and are hereby incorporated by reference in their entirety: PCT International Application Number WO 94/08051, filed October 1, 1993; "Combinatorial Approaches Provide Fresh Leads for Medicinal Chemistry," Chemical & Engineering News, Vol. 72, February 7, 1994, pp. 20-26; "A Paradigm for Drug Discovery Employing Encoded Combinatorial Libraries," Proc. Natl. Acad. Sci. USA, Vol. 92, pp. 6027-6031, June 1995; "Synthesis of a Small Molecule Combinatorial Library Encoded with Molecular Tags," Journal of the American Chemical Society, Vol. 117, No. 20, pp.

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5588-5589, 1995; "A General Method for Molecular Tagging of Encoded Combinatorial Chemistry Libraries," The Journal of Organic Chemistry, Vol. 59, No. 17, pp. 4723-4724, 1994; "Synthetic Receptor Binding Elucidated with an Encoded Combinatorial Library," Journal of the American Chemical Society, Vol. 116, No. 1, pp. 373-374, 1994; "Complex Synthetic Chemical Libraries Indexed with Molecular Tags," Proc. Natl. Acad. Sci. USA, Vol. 90, pp. 10922-10926, December 1993; "The Promise of Combinatorial Chemistry", Windhover's In Vivo The Business & Medicine Report, Vol. 12, No. 5, May, 1994, pp. 23-31.

When a compound generated using combinatorial chemistry is found to have a desirable property, it is important to be able to determine either the structure of the compound or the manner in which it was synthesized so that it can be made in large quantities. Until recently, combinatorial chemistry was practical only for generating peptides and other large oligomeric molecules because direct structure elucidation for most compounds is problematic, and such large molecules (made of repeating subunits) offered the advantage of being amenable to sequencing to determine their structure. In contrast, only very small libraries of small (i.e., nonoligomeric) molecules could be generated because, since such small molecules cannot be sequenced, the

size of the library had to be kept small enough to allow a scientist to keep track of every compound made.

Combinatorially generated peptide libraries proved to be of limited value. Peptides are poor therapeutic agents, in part because of their lack of stability in vivo. Drug companies preferred libraries of small organic molecules which, unlike most large molecules such as peptides, can frequently act when taken orally.

A need therefore existed for a scheme by which the reaction history of small molecules generated using combinatorial chemistry could be tracked. A method was developed for "tagging" the generated compounds with an identifier for each reaction step in its synthesis. The process is called the "cosynthesis" method because, as a compound is synthesized, a tag linked to the compound (or to the solid support, e.g., bead, upon which the compound is being synthesized) by means of a chemical bond is also synthesized, which encodes the series of steps and reagents used in the synthesis of the library element. When a library compound is found to have a desirable property, the tag is sequenced to determine the series of reaction steps which formed the compound. Because the tags must be sequenced, large molecule tags such as oligonucleotides and oligopeptides have been used.

The cosynthesis method has many inherent problems. For example, the tagging structures themselves are necessarily chemically labile and unstable and as such are incompatible with many of the reagents commonly used in small molecule combinatorial chemistry. Additionally, multiple protecting groups are required and the cosynthesis of a tag may reduce the yield of the library compounds. For these reasons, the cosynthesis method has not made small molecule combinatorial chemistry a commercially viable technology.

The assignee of the instant invention has developed a proprietary, pioneering technology which makes small molecule combinatorial chemistry commercially feasible. This technology is fully described in PCT published application number WO 94/08051 and employs binary coding of the synthesized compounds such that only the presence or absence of tags, and not their sequence, defines the compound's reaction history. The operation of the assignee's binary coding system is depicted in Figures 2A-2C.

Figure 2A shows a three-stage combinatorial synthesis with three reactants in each stage. While, as is known, two binary digits can uniquely identify four reactants, in a preferred embodiment, the binary digits 00 are not used to identify a reactant. Consequently, as shown



in Figure 2B, the reaction history of any compound formed in the combinatorial synthesis of Figure 2A can be represented with a six-digit binary code. The two least significant digits represent the reactant employed in stage 1, the next two digits the reactant employed in stage 2, and the two most significant digits the reactant employed in stage 3. The two digit binary code for each reactant in each stage is shown below the reactant in Figure 2A, with underlining representing bits contributed by other stages.

As shown in Figure 2C, then, compound A, which was synthesized with reactants R3, R5 and R9, can be represented with the binary code 111011. Similarly, compound B, which was synthesized with reactants R1, R6 and R8, can be represented with the binary code 101101 and compound C, which was synthesized with reactants R2, R4 and R7, can be represented with the binary code 010110.

Pursuant to the assignee's proprietary tagging technology, each of the bits of the binary code which defines a compound's reaction history is represented by a tagging molecule. These tagging molecules are bound to the solid support as the synthesis progresses such that the presence of a tag indicates that the value of the bit it represents is "1", while the absence of a tag indicates that the value of the bit it represents is "0". As illustrated in Figure 2B, tag T1 represents the least significant bit,

with successive tags assigned to successive bits such that tag T6 represents the most significant bit. As shown in Figure 2C, then, tags T1, T2, T4, T5 and T6 will be bound to the solid support on which compound A was synthesized, tags T1, T3, T4 and T6 will be bound to the solid support on which compound B was synthesized, and tags T2, T3 and T5 will be bound to the solid support on which compound C was synthesized. While, in a preferred embodiment, the assignee's binary coding technique employs tagging molecules which are bound to the solid support, those skilled in the relevant art will appreciate that the assignee's binary coding technique is not limited to this implementation, and that binary coding can be implemented with any tagging technique including but not limited to radio tagging. Radio tagging is described in "Radio Tags Speed Compound Synthesis," SCIENCE, Vol. 270. p. 577, October 1995, which is hereby incorporated by reference in its entirety.

This binary tagging technique overcomes the above referenced disadvantages of the cosynthesis method, making small molecule combinatorial chemistry feasible. As alluded to in the above referenced article titled "The Promise of Combinatorial Chemistry", however, this chemical advance has given rise to a new engineering problem, namely, how to concisely represent the contents of small molecule combinatorial libraries, each potentially containing

hundreds of thousands of unique chemical compounds, and how to plan their generation such that the probability of generating compounds with useful characteristics is increased. Existing systems, such as those developed by Tripos, Inc. ("Tripos"), MDL Information Systems, Inc. ("MDL") and Daylight Chemical Information Systems, Inc. ("Daylight") are either infeasible or impractical for use with small molecule combinatorial libraries because the representation schemes implemented by these systems do not allow for concise representations of all types of small molecule combinatorial libraries, for tracking of those libraries which are binary coded or for correct enumerations of those libraries generated on solid support.

In the MDL system, the operation of which is described with reference to Figures 3A-3D, a combinatorial library is represented with

- 1) one core chemical structure having attachment points for chemical moieties which are added or attached to the core structure at each stage of the combinatorial synthesis; and
- 2) lists of the moieties which can be added to the core structure at each stage ("additions").

An example of an MDL representation of a combinatorial library is shown in Figure 3A. The core structure is shown with attachment points R1-R4, representing points of attachment for moieties which can be added to the core

structure in stages 1-4 of the combinatorial synthesis respectively. Also shown are four lists of structures, each list representing the compounds which can be added to the core structure in one of the four stages. The point of attachment of each compound added to the core structure is indicated with a dot. The contents of the combinatorial library can be enumerated by identifying all permutations of the compounds of the four lists as attached to the core structure. As used in this specification, the term "enumeration" will mean the process of generating representations of the entire structure of each of the compounds in the library based on the concise representation employed by a system.

The MDL system has many limitations which render it infeasible for use with small molecule combinatorial chemistry. For example, each addition can have at most two attachment points. While suitable for peptide chemistry, two attachment points per addition are insufficient to represent the structures contained in many small molecule combinatorial libraries. For example, the MDL system would be unable to represent a core structure such as that shown in Figure 3B, since the moiety R2 has three points of attachment.

Another limitation of the MDL system which makes it infeasible for use with small molecule combinatorial chemistry is that all the possible additions at each reaction stage must attach at the same point or points on the core structure. It is possible in small molecule combinatorial synthesis to have different additions at a given reaction stage which attach at different points on the structures generated in previous stages.

Furthermore, the MDL system cannot represent additions which attach only on a subset of the structures formed in previous reaction stages. An example of such a library is shown in Figure 3C, where a core structure of a combinatorial library can be seen along with a subset of the additions possible from stages 1 and 2. Since the first addition from stage 2 attaches only if the second addition from stage 1 attaches, the MDL system could not represent the library, since all additions from all stages must attach directly to the core structure in the MDL system. Since substituents from a given stage may or may not attach depending on the identities of the substituents attached during previous stages, this limitation also renders the MDL system unsuitable for use with small molecule combinatorial chemistry.

Finally, there are many ways in which small molecule combinatorial libraries can be generated for which a single core structure cannot be defined and which, consequently, cannot be represented by the MDL system. For example, if the possible additions at each of the first three stages are as shown in Figure 3D, where the black boxes are used to represent chemical structures and the numbered bonds represent points of attachment, the MDL system could not represent the library. No single core structure can be defined to which all the possible additions from all the stages attach. Rather, in the example of Figure 3D, two core structures are required, depending on whether the first or the second addition from R2 attaches to the addition from R1.

The Tripos system is similar in many respects to the MDL system, and is similarly incapable of concisely representing all types of small molecule combinatorial libraries. For example, like the MDL system, the Tripos system requires that a common core structure be defined, and like the MDL system, it cannot handle combinatorial chemistry where additions attach only to a subset of the structures formed in previous stages. Although in some respects the Tripos system is more flexible than the MDL system (e.g. all additions from all stages need not link directly to the core), it is in many respects even more

limiting than the MDL system. For example, the core structure of the Tripos system must be well defined in that it cannot be made up of all variables. This severely limits the types of chemistry with which it can be used because, as discussed above, defining a core structure can be problematic. In short, for many of the same reasons discussed with respect to the MDL system, it is infeasible to use the Tripos system as a tool for representing the contents of small molecule combinatorial chemistry libraries.

The Daylight system, while purportedly designed to represent combinatorial libraries, does not solve the problem of concisely representing small molecule libraries in such a way that a chemist, from the concise representation alone, can understand the makeup of the library. In order to represent the contents of these libraries concisely, Daylight employs several levels of indirection, meaning the "concise" representation is actually useful only as an index into a database from which the contents of the library can ultimately be discerned. The operation of the Daylight system is illustrated in Figures 4A-4E.

In the Daylight system, monomers are assigned arbitrary names by the user, and are represented and stored in the system using a linear representation of the atoms of the monomer as demonstrated in Figure 4A. The atoms are listed in the linear representation in the order in which they bind, with branches indicated in parentheses. Atoms to which other monomers bind, or which serve as the point of a ring closure on the monomer, are labeled with numbers appearing to the immediate right of the atom. When the final polymerized structure is enumerated, paired number labels internal to the monomer definition will be bound together first, after which like labels will be bound together from left to right in the order in which they appear. Because each monomer is independently defined, and it is impossible to know a priori the location in the polymerized structure at which any atom will bind, each monomer contains number labels from 1-N, and the representation scheme for the polymerized structure provides for substitution of these labels with labels indicating the attachment points in the polymerized structure. Figure 4A shows the chemical structure for three monomers, the manner in which they are represented with the Daylight linear representation scheme, and arbitrary names which can be assigned to the monomers by the user. The sulfur atom in the "Cys" monomer has a label of 1. Since no other atom in



Cys is labeled with a 1, which would indicate points for a ring closure, the sulfur atom can serve as a point of attachment to other monomers.

5                   Figure 4B demonstrates how a polymerized molecule can be represented in the Daylight system using linked monomer names. Also shown in Figure 4B is the Daylight linear representation of these linked monomers, and the actual chemical structure of the polymerized molecule represented. Note that while the sulfur of every Cys  
10 monomer is not required to serve as a point of attachment, the two that do are bound at the sulfurs with like labels of "1".

                  Figures 4C and 4D present a more detailed example of the way monomers are represented in the Daylight system.  
15                   Figure 4C illustrates the way five monomers are represented by Daylight's linear representation scheme and arbitrary user-assigned names for each. The first monomer of Figure 4C shows both ring binding indicators, which occur in pairs (the numbers 7, 8 and 9 in the first structure of Figure 4C, indicated in grey), and unpaired numbers indicate points of  
20 attachment with other monomers (the numbers 1-4 in the first structure of Figure 4C, indicated in underlining). As can be seen with respect to this monomer, which has been named "Pam" by the user, a lower case "c" represents a carbon of  
25 an aromatic ring and an upper case "C" represents a carbon

of a non-aromatic ring. Single atom monomers do not require labels to indicate that they can serve as points of attachment, since they have only one possible point of attachment.

5                   Figure 4D demonstrates how the contents of a combinatorial library can be represented as a string of monomer names separated by periods (additional monomers, besides those defined in Figure 4C, are used for purposes of the example). Monomer names followed by numbers in a  
10                   polymerized compound or library definition indicate, by their order, the numbers which should be substituted for the numbers in the monomer definition. Thus, "Pam2768"  
indicates that the number in the first position following the monomer name, "2", should be substituted for the number  
15                   "1" in the monomer Pam. Similarly, the number in the second position following the monomer name, "7", should be substituted for the number "2" in the monomer Pam, and so on. The identities of possible additions "2", "7", "6" and  
20                   "8" are listed in brackets before each of the respective numbers. Figure 4E shows a Daylight representation of a partial enumeration of the library of Figure 4D, as well as the chemical structure it represents.

As is intuitively clear, a scientist could not look at a library representation such as

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Pam2768. [Brx;Clx;Fx;Hx;Ix] 2. [Clx;Fx;Hx;Nitrox] 7.  
[Eohx;Etx;Hx;McpX;Mex;Mohx;Phex;Ppox;Tfex;Tppx] 6.  
[Carx;Hx;Ohx] 8

5 and obtain a conceptual understanding of the contents of the  
library. To obtain such an understanding of the library,  
the scientist would have to:

- 10 1) Index the database to determine the linear  
representations for each of the linked  
arbitrary monomer names in the library  
representation;
- 15 2) Draw out the chemical structure of the  
monomers represented by each linear  
representation; and
- 20 3) Substitute the number labels in the library  
definition for the number labels in the  
monomer definition.

The Daylight system also has some of the same  
deficiencies as do the MDL and Tripos systems. For example,  
it is incapable of representing substituents which attach  
25 only on a subset of the structures formed in previous  
reaction stages. When substituents do not attach, the  
Daylight system will nevertheless show the unattached  
substituents as distinct members of the enumerated library,  
which is particularly unsuitable for use with the assignee's  
30 binary coding tagging technology as used with solid phase  
synthesis, wherein all unattached molecules are washed away  
and do not become part of the library. Additionally,  
neither the Daylight system nor the MDL or Tripos systems

provide facilities for keeping track of small molecule combinatorial libraries generated with binary coding.

Planning the design of a library with molecules having desired characteristics has also proven to be  
5 difficult because there exists no computationally feasible deterministic method for selecting starting molecules and reactants with which a diverse small molecule combinatorial library having such characteristics will be created. The manner in which synthons (starting molecules and reactants  
10 collectively may be referred to as "synthons") are generally selected, and the limitations therewith, are detailed in U.S. Patent No. 5,463,564 to Agrafiotis et al., issued on October 31, 1995 (the "'564 patent"), which is hereby incorporated by reference in its entirety. The solution  
15 described in the '564 patent involves iteratively:

- 1) robotically synthesizing "directed diversity" chemical libraries;
- 20 2) analyzing the compounds created in step (1);
- 3) storing structure-activity data for the compounds created;
- 25 4) comparing the structure-activity data for the compounds created with those desired for the library;
- 30 5) assigning rating factors to the synthons based on how close the generated library is to the desired library;

- 5                   6)     analyzing the structure-activity data to select  
                      which synthons will produce libraries with  
                      properties closer to the desired library; and
- 7)     generating computer instructions such that the  
                      next iteration will utilize the synthons selected  
                      in step (6).

10           There are many drawbacks with the system described in the  
              '564 patent, including but not limited to the following:

- 15                   1)     chemical libraries must be generated repeatedly, a  
                      process which may be impractical based on the  
                      limited availability of the necessary compounds  
                      and reactants. To the extent it is feasible, the  
                      process will be very expensive, particularly in  
                      light of the fact that many synthons which  
                      ultimately may turn out to be superfluous will be  
                      required;
- 20                   2)     it is not especially useful with combinatorial  
                      chemistry, but rather implements what is  
                      explicitly described as a different process  
                      altogether, namely "directed diversity" chemistry  
                      (Col 5 lines 1-22);
- 25                   3)     it does not describe a solution useful with small  
                      molecule chemistry, but rather states that "[t]o  
                      date, most work with combinatorial chemical  
                      libraries has been limited only to peptides and  
                      oligonucleotides ..." (Col 2 lines 32-34) and that  
                      "[t]he peptide synthesis technology is preferred  
                      in producing the directed diversity libraries  
                      associated with the present invention"; and
- 30                   4)     while a computer is described for evaluating the  
                      characteristics of the library generated vis-a-vis  
                      the desired library, no scheme is contemplated or  
                      described for graphically representing the  
                      contents of the generated library such that a  
                      scientist could quickly understand exactly what  
                      compounds were produced.
- 35
- 40

It is also highly questionable whether a system such as that described in the '564 patent could actually be built.

The following articles, each of which is hereby incorporated by reference in its entirety, also describe methods for selecting starting molecules and/or criteria used in their selection: "Measuring Diversity: Experimental Design of Combinatorial Libraries for Drug Discovery," Journal of Medicinal Chemistry, Vol. 38, No. 9, pp. 1431-1436, 1995 by Martin et al.; "A Nonlinear Map of Substituent Constants for Selecting Test Series and Deriving Structure-Activity Relationships. 1. Aromatic Series," Journal of Medicinal Chemistry, Vol. 37, No. 7, pp. 973-987, 1994; "Hydrogen Bonding. 32. An Analysis of Water-Octanol and Water-Alkane Partitioning and the  $\Delta \log P$  Parameter of Seller," Journal of Pharmaceutical Sciences, Vol. 83, No. 8, pp. 1085-1100, 1994. However, none of these references describe an automated or semi-automated system for use with combinatorial chemistry or, for that matter, the application of evaluation criteria to a proposed combinatorial library.

There is, therefore, a need for a system and method which provides a concise and accurate representation of the contents of actual or planned small molecule combinatorial libraries created with solid phase synthesis. Additionally, there is a need for a system and method useful for planning the development of small molecule combinatorial

libraries. Finally, there is a need for a system and method which combines these two capabilities such that synthons can be automatically and intelligently selected, and the library which would be combinatorially created therewith evaluated such that the results of the evaluation add to the intelligence with which synthons will be selected in the future.

#### SUMMARY OF THE INVENTION

It is an object of the present invention to provide a concise representation of the contents of any combinatorial chemical library.

It is another object of the present invention to produce an accurate enumeration of the contents of any combinatorial chemical library generated on solid support.

It is another object of the present invention to provide a tool for tracking the contents of any combinatorial chemical library labeled with binary coding.

It is another object of the present invention to provide a combinatorial chemical library planning tool for automatically and intelligently selecting synthons without performing a chemical synthesis.

It is another object of the present invention to provide a combinatorial chemical library planning tool for automatically and intelligently selecting synthons without

performing a chemical synthesis, and thereafter automatically generating a concise representation of the combinatorial library which would be created therewith.

5 It is another object of the present invention to provide a combinatorial chemical library planning tool for automatically and intelligently selecting synthons without performing a chemical synthesis, automatically generating a representation of the combinatorial library which would be created therewith, evaluating this representation and  
10 improving the intelligence with which synthons are selected as a function of this evaluation.

It is another object of the present invention to provide a combinatorial chemical library planning tool for automatically and intelligently selecting synthons without  
15 performing a chemical synthesis, automatically generating a representation of the combinatorial library which would be created thereby, automatically evaluating this representation and improving the intelligence with which synthons are selected as a function of this evaluation.

20 Further objects and advantages of the present invention will be clear to those skilled in the art from the ensuing detailed description.



### DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the manner in which combinatorial chemistry allows for a large library of diverse molecules to be generated with a small number of reaction steps;

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Figures 2A-2C illustrate the assignee's proprietary binary coding technology;

Figures 3A-3D illustrate the manner in which the MDL system operates;

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Figures 4A-4E illustrate the manner in which the Daylight system operates;

Figures 5A-5E illustrate a preferred embodiment of two representations of a small molecule combinatorial library pursuant to the instant invention;

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Figure 5F represents an alternative embodiment of the present invention which includes selective combination, as that term is defined hereafter;

Figure 6 illustrates the operation of a preferred embodiment of the starting molecule selection method and apparatus of the instant invention.

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### DETAILED DESCRIPTION

While the instant invention is described with particular reference to libraries of small molecules, it will be understood that the invention is useful with all

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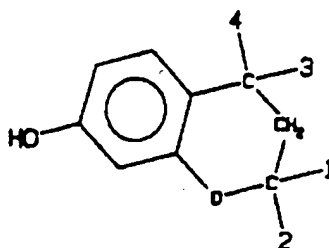
combinatorial libraries including, but not limited to, libraries in which additions or contributions can have more than two attachment points. The same features which make the invention particularly useful for small molecule combinatorial chemistry are advantageous for use with all types of combinatorial chemistry.

One object of the present invention is to provide a concise representation of small molecule combinatorial libraries. An example of the use of our invention for this purpose is shown in Figures 5A-5E.

R1-R4 in Figure 5A represent four reaction stages. The chemical structures shown for each stage represent the contributions made by the synthons utilized in that stage, i.e., the contribution of the synthon is the portion of each synthon ultimately incorporated into a member of the library, as well as the manner in which these contributions can be pieced together with the contributions of the other stages. In this way, our system differs markedly from the MDL and Tripos systems, as those systems begin with a single core structure, while our representation allows for an unlimited number of contributions in the first step to accurately reflect the manner in which the library compounds are synthesized. The contribution would not include, for example, portions of the synthon which react to form by-products that are "washed away" during the synthesis

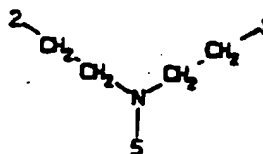
process. Every structure of R1 is combined with every structure of R2 (as long as there is a place for the respective structures to attach to one another, as will be explained below). Every resulting structure R1 + R2 is combined with every structure of R3, and every structure R1 + R2 + R3 thereby created is combined with every structure of R4 (again, as long as there is a place for the respective structures to attach to one another). The structures R1 + R2 + R3 + R4 thus created represent the library of molecules combinatorially formed.

The manner in which structures are combined is indicated by like labels, in a preferred embodiment like numbers, in the structures. The numbers label the bonds themselves. For example, the first structure of R1



may be combined with the first structure of R2

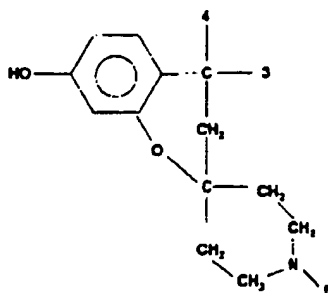
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5

at numbers "1" and "2" (i.e., the two labels which are identical in the two structures of R1 and R2 under discussion) to form

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The numbers 3, 4 and 5 are labels used to indicate the positions at which the particular structure R1 + R2 under discussion may combine with the contributions of stages R3 and R4.

It is readily apparent that this representation overcomes the limitations described above with respect to the MDL, Tripos and Daylight systems. For example, no single "core" structure is required, substituents can have

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any number of attachment points, and substituents from later stages can attach at any point on structures from previous stages. In addition, this present method of concisely representing the contents of small molecule combinatorial libraries does not employ indirection, making it possible for a scientist to view the contents of the entire library without the need for any cross-referencing. This aspect of our invention can be implemented using commercially available packages for representing chemical structures, or can be routinely implemented using conventional programming techniques by those having ordinary skill in the relevant art. In any case, this aspect of our invention is directed to the manner in which the library is represented and not to any particular implementation of the representation scheme.

In an additional embodiment of the invention, our representation technique takes into account the fact that certain reaction products from certain stages of the reaction may not be combined with certain of the synthons in the next stage. The combination may be impossible (e.g., because the reaction will not occur) or simply undesirable (e.g., because such reaction products are intended to be excluded from the library).

The latter situation contrasts with combinatorial chemistry techniques generally utilized today which, in their most elementary form, mix every molecule formed during

reaction stage N with every synthon from reaction stage N + 1. However, as will be more fully described hereafter, in certain instances, it is desirable or possible to mix with the synthons of reaction stage N + 1 only some of the molecules formed during reaction stage N. Alternatively, it may be desirable or possible to mix all molecules formed during reaction stage N with only some of the synthons of reaction stage N + 1. In general, some or all synthons from any reaction stage (other than the very first reaction stage) may be combined with some or all of the products from any previous reaction stage, and certain reaction steps can be omitted. We term these situations "selective combination."

In order to more accurately represent and track molecules generated combinatorially via selective combination, an additional improvement to the present invention has been developed. A technique has been developed to tag, track, and represent combinatorial libraries, and enumerate the resulting chemical structures, which easily and compactly conveys and records the selective combination (e.g., the omitted reaction steps).

In addition to recording and conveying information regarding the omitted reaction steps, our technique allows for the generation and representation of what we term biased libraries. Specifically, it may be desirable to divide the

synthons of a reaction stage into subsets, and to then react different proportions of the products of a previous reaction stage with each subset. For example, if reaction stage 2 is divided into two subsets of synthons, it may be desirable to react 80% of the products from reaction stage 1 with the first subset of synthons from R2, while reacting only 20% of the products from reaction stage R1 with the remaining subset from reaction stage R2.

The foregoing technique allows the biasing of particular reaction stages. The technique is useful in that the scientist may desire to generate more products containing certain synthons than containing other synthons. In the foregoing example, more products will be generated which result from combinations of the contributions from R1 with the synthons in the first set of R2 (with which 80% of R1 contributions are reacted) than will be generated as a result of combinations between the contributions of R1 and the second subset of R2 (with which only 20% of R1 contributions are reacted).

It is also within the scope of the invention to use such biasing to create a more equal distribution of final products in some cases where certain synthons or products may have been present in disparate proportions. For example, if, stage R1 includes 33 1/3% R1.1 and 66 2/3% R1.2, equal distribution may be obtained through the use of

biasing. Presuming stage R2 is divided into two subsets,  
the first of which reacts with R1.1, and the second of which  
reacts with R1.2, twice as much R1 would be reacted with the  
first subset of R2 as would be reacted with the second  
5 subset of R2. This would equalize the amount of the  
resulting compositions.

Figure 5F shows one embodiment of the novel  
representation scheme to represent and track the generation  
of a combinatorial library produced via selective  
10 combination of contributions from the four stages of Figure  
5A. As can be appreciated from Figure 5F, the technique  
immediately and conveniently conveys the fact that all of  
the products of reaction stage R1 are pooled and then  
divided into aliquots of 50%, 30%, and 20%. The 50% aliquot  
15 is further divided into portions of 25%, 35%, and 40% which,  
respectively, are reacted with the synthons corresponding to  
the contributions R2.1, R2.2, and R2.3 in stage R2 to form  
structures R1.1R2.1, R1.1R2.2, R1.1R2.3, R1.2R2.1, R1.2R2.2,  
R1.2R2.3, R1.3R2.1, R1.3R2.2, and R1.3R2.3. All of these  
20 structures are then reacted with all the contributions in  
stage R3, and the resulting products are all reacted with  
all of the contributions in stage R4.

The 30% aliquot from stage R1 is reacted with the  
synthons corresponding to the contributions R2.4, R2.5,  
25 R2.6, and R2.7 in stage R2. (As indicated in Figure 5F, 20%



of such aliquot is reacted with R2.4; 35% of such aliquot is reacted with R2.5; 15% of such aliquot is reacted with R2.6; and 30% of such aliquot is reacted with R2.7). The resulting structures are not reacted with any of the contributions from stage R3, but are reacted directly with the contributions from stage R4. Finally, the 20% aliquot from stage R1 is not reacted with any contributions from either stage R2 or R3, but is reacted directly with all the contributions from stage R4.

From the foregoing it is clear that reaction stage R2 is divided into subsets of synthons. Each distinct subset will have a reaction history different from that of other distinct subsets. When a computer is tracking or representing the library generated by the reactions shown in Figure 5F, the computer may be programmed to associate certain tagging molecule(s), respectively, with each synthon in each reaction stage. By checking for the presence or absence of tags from a particular reaction stage, the computer can reconstruct the reactions which actually occurred according to the representation in Figure 5F, and can ultimately determine both the structures of the resulting molecules as well as the procedure for generating these.

Additionally, the biasing technique previously discussed is shown in Figure 5F, and may be represented with the novel technique as well. Between each subset of contributions and a subsequent subset of contributions with which said subset will combine, there is shown a link labelled with a percentage. The percentage represents the portion of the products from the earlier reaction stage to be reacted with the synthons in a subsequent reaction stage. For example, link 504 indicates that 50% of the products of R1 will be reacted with the subset of R2 that contains R2.1, R2.2, R2.3. Similarly, each of the contributions R2.1, R2.2, and R2.3 in Figure 5F is labelled with a percentage representing the further allocation of the products from link 504 to the reactions with R2.1, R2.2, and R2.3 (i.e., 25%, 35%, and 40%, respectively). The computer used to generate and store representations of the combinatorial libraries may also store the values associated with each link and each further allocation. Thus, when the tags identifying a resulting molecule are input, the computer can determine the molecule's chemical structure and the combinatorial method used to generate the molecule.

The aforementioned description permits the benefits of combinatorial chemistry to be utilized while avoiding the necessity of mixing every product resulting

from a reaction stage with every synthon from the next stage, in equal amounts.

5 It is another object of the present invention to produce an accurate enumeration of the contents of small molecule combinatorial libraries generated on solid support. Our invention accounts for the fact that small molecule combinatorial chemistry was made feasible by the assignee's binary coding technique, and that this technique was initially developed for solid phase synthesis. For example, 10 the fact that certain contributions need not bind with all of the compounds formed in previous stages in small molecule combinatorial chemistry performed on solid support had to be understood and accounted for. In solid phase chemistry, contributions which do not bind to a compound generated in a 15 previous phase will be "washed away," meaning that the synthon will not attach to the solid support at all and thus will not be incorporated into certain compounds in the final combinatorial library. For example, when any of the last three structures of R2 in Figure 5A is chosen as the 20 contribution for R2, there will be no place for any of the substituents in R3 to attach, and consequently the substituents in R3 would be considered "washed away" and not included in the final library of compounds. This is in contradistinction to chemistry performed in solution, 25 whereby unattached compounds will be present in the

combinatorial library in "free floating" form. Our invention will not include free floating compounds in the representation of the library it generates when enumerating structures synthesized on solid support, since such

5 compounds are not present in small molecule combinatorial libraries generated on solid support. Existing systems do not account for this or other differences between solid phase chemistry and chemistry performed in solution. Our system was designed to accurately enumerate any

10 combinatorial library, including, but not limited to, all small molecule combinatorial libraries generated on solid support.

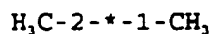
Thus, with reference to Figure 5A, it is noted that molecules containing any of the last three potential

15 contributions shown for reaction stage R2 cannot attach to any contribution in reaction stage R3 because none of these last three R2 contributions includes an attachment point labeled "5," while a review of all six potential contributions in R3 shows that none of them includes

20 attachment points labeled "1" or "2". Accordingly, any structure resulting from a combination of an R1 contribution with one of the last three contributions of R2 cannot include a contribution from R3.

Consider the second contribution shown for R1 which could combine with the fifth contribution shown for R2. The resulting structure would include three rings, the first two being the alicyclic and aromatic moieties already present in the second contribution of R1, and the third ring resulting from the attachment, at points labeled "1" and "2," of the fifth contribution in R2 to the carbon atom with labels "1" and "2" in the second contribution of R1. The resulting molecule has attachment points "3" and "4", which could serve to form a fourth ring with the first contribution of R4. However, the reaction stage R3 is effectively skipped because, although the molecules resulting from reaction stage R2 are physically mixed with the contributing synthons of R3, no chemical reaction can take place.

Furthermore, a contribution in a stage may actually be two or more unattached compounds, a possibility which we account for in our representation scheme by separating unattached compounds with a "\*". For example, the last structure of R2 in Figure 5A:



represents that a CH<sub>3</sub> group is to be attached at both position numbers "1" and "2" of the structures from stage 1. Any

number of unattached compounds can be represented in a structure by depicting these as attached to the "\*" or by using multiple "'s".

5 It is another object of the present invention to provide a tool for tracking the contents of small molecule combinatorial libraries generated with binary coding. Applicants have discovered, by use of assignee's proprietary binary coding technique, that such a tool is necessary if large libraries of small molecules are to be successfully managed and tracked, and have invented a system and method for  
10 managing and tracking such libraries. This system and method has the capabilities of:

15 1) encompassing within the representation of each contribution a representation of the tag or tags associated with the synthon making such contribution;

20 2) inputting into the system the representation of a tag or tags (as well as identification of a library if the system contains more than one library) and outputting to the user a representation of the contribution made by the synthon associated with the tag or tags;

25 3) inputting into the system the representation of a tag or tags (as well as identification of a library if the system contains more than one library) and outputting to the user a representation of the synthesized compound or compounds produced on the solid support to which such tags are bound.  
30

These features are described seriatim.

Figures 5B - 5E show a representation of the same small molecule combinatorial library depicted in Figure 5A,

but include with the representation of each contribution the tags associated with such contribution. As shown in Figures 5B - 5E, for example, the numbers immediately following the "R" (hereinafter referred to as the "R number") uniquely identify each potential contribution, with the number preceding the period indicating the stage and the number following the period indicating the substituent chosen from that stage. Thus, "R1.2" indicates the second member of the set of potential contributions from stage 1, "R2.5" the fifth member of the set of potential contributions from stage 2, and so on. The actual names of the contributing synthons or definitions of the chemistry by which they were created are not included in a preferred embodiment because they are not necessary in order to view and understand the contents of a small molecule combinatorial library. However, those skilled in the relevant art will appreciate that the names of the contributing synthons or definitions of the chemistry by which they were created could just as easily be included in the representations shown in Figures 5B-5E if they are considered relevant or useful.

Following the R number is a colon, after which a list of the tags associated with the contributing synthon appear, separated by semicolons. Tags are "associated" in the present invention by virtue of the fact that presence of a tag implies presence of the contribution from a particular

synthon. The association can be physically maintained by simply indicating, in a computer, which tags imply the presence of which molecules.

5 In a preferred embodiment, the tags are identified by distinguishing characteristics of the tagging molecules. For example, "C10 Cl5" refers to a tagging molecule which has ten carbon and five chlorine atoms. However, those skilled in the relevant art will appreciate that any method can be used for identifying the tags associated with a contributing  
10 synthon, and all fall within the scope of the present invention.

The present invention also includes an input device into which the tag or tags associated with a contributing synthon can be entered, and an output device onto which the  
15 corresponding contribution can then be displayed. Similarly, the present invention provides for entry of a contributing synthon identifier, which will cause the tag or tags associated with the contributing synthon to be displayed. While, in a preferred embodiment, the format in which tags and  
20 contributions or contributing synthons are entered and/or displayed are as shown in Figures 5B-5E, those skilled in the relevant art will appreciate that any method for entering and/or displaying this information can be used, and the present invention should not be deemed to be limited by any



method and/or medium for entry and/or display of tag or synthon information.

The present invention also includes an input device into which can be entered a representation of the tag or tags bound to the solid support on which a combinatorial library member was synthesized, which will cause to be displayed the chemical structure of that library member. In a preferred embodiment, the tag or tags bound to the solid support are entered using distinguishing characteristics of the tagging molecules as illustrated in Figures 5A-5E, and the display used for a library member is its actual chemical structure. However, those skilled in the relevant art will appreciate that any method and/or medium can be used to enter the tag information or to display the library member information, and the present invention should not be deemed to be limited by any method and/or medium for entry of tag information and/or display of library member information.

It is another object of the present invention to provide a small molecule combinatorial library planning tool for automatically and intelligently selecting synthons without performing a chemical synthesis. In a preferred embodiment, this is achieved by utilizing an expert system for which the criteria used by scientists to select synthons serves as the initial knowledge base, although those skilled in the art will recognize that any computational system can be utilized.

Figure 6 shows the components and steps which make up this aspect of the present invention.

As is understood by those skilled in the relevant art, a knowledge base contains rules and facts which are used by the expert system to draw conclusions. The knowledge base of the instant invention, depicted in Figure 6, contains rules and facts to be applied in the selection of synthons. The knowledge base of a preferred embodiment of the present invention is initialized with rules obtained from subject matter experts.

Table 1 contains a partial list of compound characteristics which typically are used by chemists to select synthons, along with brief comments regarding the application of each characteristic. For example, if a combinatorial library of lipophilic compounds is desired, synthons which are lipophilic will be selected. Methods for calculating lipophilicity are described in the Martin et al. article incorporated by reference hereinabove. These and other rules regarding the types of synthons to select in order to obtain given characteristics in the target library are incorporated into the knowledge base of the present invention. Those skilled in the relevant art will appreciate that many different rules can be incorporated into the knowledge base, and the scope of the present invention is not limited to a knowledge base containing any one or more rules.

TABLE 1

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Lipophilicity (in general a desirable range for the lipophilicity of finished compounds is between 0 and 5)
Hydrogen Bonding Ability (measured by the number of heteroatoms)
Molecular Weight (the molecular weight of the most preferred finished compounds is less than 700)
Diversity of Atom Descriptors (a library of finished compounds should not be concentrated in a particular class along any of the commonly used atom-pair or atom-torsion descriptors, but rather should make up a diverse set)
Polyaromatics (are generally undesirable in a library of finished compounds because they are considered to be cancer-causing agents)
Anilines (are generally undesirable in a library of finished compounds because they are typically toxic)

25

30

As shown in Figure 6, scientists 604 generate the rules with which the knowledge base 601 of the expert system 603 is initialized. Two rules which might be included in the knowledge base are expressed as Rules 1 and 2 below. These rules are written in pseudocode, but those skilled in the relevant art will appreciate that these rules can be easily translated into the syntax of any of the commercially available expert system shells, expert system toolkits or programming languages with which rules can be represented:

35

/\* Rule 1 \*/

IF (target library lipophilicity  $\geq$  X) THEN select synthons  
whose lipophilicity  $\geq$  f(X)

/\* Rule 2 \*/

5

f(X) = X

Using Rules 1 and 2, if a scientist wants a combinatorial library  
created with compounds having a lipophilicity of X or greater,  
10 synthons will be selected whose lipophilicity is greater than or  
equal to some function of X, where this function of X is defined by  
Rule 2 to be equal to X itself. Referring again to Figure 6, the  
lipophilicity criteria of the target library are selected by  
chemist 606, and are entered into the expert system via input  
15 device 605, which in a preferred embodiment is a computer or a  
computer terminal.

Inference engine 602, as will be readily understood by  
those skilled in the relevant art, is the control module of the  
expert system. It reads the rules in the knowledge base and forms  
20 conclusions and takes actions based thereon. Thus, if Rules 1 and  
2 above were the only rules in the knowledge base, inference engine  
602 would read these rules and select from the database of synthons  
607 all which have a lipophilicity of greater than or equal to the  
value X selected by chemist 606. Similar rules and techniques can  
25 be used to select the contributions desired from subsequent stages.

Using techniques and criteria such as those described, a  
proposed library 608 is automatically generated by the expert  
system 603. This library can be represented as a set of synthons

for stage 1 and synthons for stages 2-N. Alternatively, the library can be represented as the contributions possible from each stage of the synthesis. Those skilled in the relevant art will appreciate that many different techniques and criteria can be used to generate a representation of the proposed library, and this aspect of the present invention is not limited to any one or more techniques or criteria.

Although the format for representing the proposed library can vary, in a preferred embodiment the representation used is that which we developed, described above, for concisely representing the contents of small molecule combinatorial chemistry libraries. One reason for use of our library representation with this aspect of the invention in a preferred embodiment is that it can be shown to a chemist 606 who, based on a visual inspection of same, can quickly evaluate whether the library has the desired characteristics. If the library does not, the chemist can evaluate whether the rule base needs to be modified and, if so, it may be modified accordingly as shown in step 621. Alternatively, the chemist may decide the rules are satisfactory, but that the characteristics of the target library should be modified. In this case, he can define new characteristics and enter them into the expert system 603 via input device 605 as shown in step 622.

As shown in Figure 6, the present invention also contemplates evaluating the proposed library automatically. In a preferred embodiment, in which our library representation is used,

the enumeration component of that aspect of the invention is used to enumerate the proposed library in step 610 of Figure 6. This causes a representation of all proposed synthesized compounds 611 to be automatically generated.

5           The representation of all proposed synthesized compounds can then optionally be statistically sampled, as shown at step 612 of Figure 6. This statistical sampling will produce a subset 613 of the representations of all the proposed synthesized compounds 611. This statistical sampling can be performed automatically  
10 using any sampling methodologies, including but not limited to random sampling. The advantage of employing statistical sampling is that, by reducing the number of compound representations on which the compound evaluation algorithms 614 must be run, the computational resources required by such compound evaluation  
15 algorithms is reduced.

          The compound evaluation algorithms 614 utilize known computational methods for measuring characteristics of compounds, such as those identified in Table 1. Examples of such computational methods are described in the Martin et al. reference  
20 incorporated by reference hereinabove, although those skilled in the relevant art will recognize that other such computational methods exist, and that the present invention is not limited to use of the methods described in the Martin et al. reference. These algorithms generate coefficients for the enumerated library 615  
25 which are compared in step 616 to the criteria 600 (e.g.,

diversity) defined for the coefficients of the target library. If the coefficients for the enumerated library do not satisfy the criteria defined for the coefficients of the target library when they are compared in step 616, the rules of the knowledge base are updated as shown in step 618 to reflect the information learned from the results of the compound evaluation algorithms. For example, if the lipophilicity of the target library was defined to be 2 or greater and the lipophilicity of the enumerated library is 1, the lipophilicity of the synthons utilized must be increased. One way to do this would be to modify Rule 2 in the example above to make  $f(X)$  greater than  $X$ , e.g.,  $f(X) = X + 1$ .

If the coefficients for the enumerated library do satisfy the criteria defined for the coefficients of the target library, the library represented is made and screened as shown in step 619. This testing of the synthesized library for desirable properties will itself provide information with which the rules of the knowledge base can be updated as shown in step 620. These rules will include those which relate enumerated library coefficients to target properties. For example, it may be learned that synthesized compounds with a high lipophilicity uniformly or with great regularity provide hits against certain biological targets. This information can, either automatically or manually, be incorporated into the rules of the knowledge base such that scientists defining the target characteristics of other libraries would need to identify only the target to be screened, and the expert system

would be able not only to deduce that such characteristics as lipophilicity are applicable to that target, but also to apply the relevant lipophilicity criteria which have previously produced hits for that target. Such criteria would be utilized, inter alia, by  
5 the system in the selection of synthons for the generation of a library containing molecules having the desired characteristics.



**WE CLAIM:**

1. A method for representing a combinatorial chemistry library comprising:

5 (a) representing, for each stage in the combinatorial reaction series, the set of chemical structures of the contributions made, respectively, by each potential synthon in such reaction stage, i.e., the portion of such synthon which ultimately could be incorporated into a member of such combinatorial library.

10

2. The method of claim 1, further comprising:

(b) indicating, in each chemical structure represented in (a), every position at which such chemical structure may attach to another chemical structure which corresponds to the contribution made by another synthon  
15 utilized in a different reaction stage.

3. The method of claim 2, wherein one or more of said chemical structures contain more than two positions for attachment  
20 to other chemical structures.

4. The method of claim 2, wherein said combinatorial chemistry library is encoded with tags and said representing comprises identifying, for each such chemical structure, one or  
25 more tags which uniquely identify such chemical structure.

5. The method of claim 4, wherein said tags comprise tagging molecules.

6. The method of claim 5, wherein said identifying one or more tags comprises identifying distinguishable characteristics of said tagging molecules.

7. The method of claim 2, wherein said indicating of positions of attachment to contributions from other stages comprises labeled bonds.

8. The method of claim 7, wherein said labeled bonds comprise numbered bonds.

9. The method of claim 3 further comprising:

(c) enumerating said combinatorial library representation by attaching, at the indicated positions of attachment, a single member of the set of chemical structures for a reaction stage to a single member of the set of chemical structures for a different reaction stage, so as to represent the entire structure of one or more compounds in said combinatorial chemistry library.

10. The method of claim 9 wherein said combinatorial chemistry is performed on solid support and wherein said enumeration omits any and all unattached contributions.

5 11. A method for performing combinatorial chemistry comprising:

(a) associating with each potential synthon in each stage of a combinatorial synthesis one or more tags uniquely identifying such synthon;

10

(b) linking to each compound synthesized from such synthon, or to a solid support upon which said compound is being synthesized, one or more tags uniquely identifying such synthon so that the reaction history of each compound in the resulting combinatorial chemistry library is defined by which tags are linked thereto;

15

(c) entering into a computerized system a representation of a first set of one or more tags; and

20

(d) displaying on an output device a representation of a first compound identified by said first set of one or more tags.

12. The method of claim 11 wherein said one or more tags comprise radio tags.

25

13. The method of claim 11 wherein said first compound comprises the entire structure of one compound in said combinatorial chemistry library.

5           14. A method for performing combinatorial chemistry comprising:

(a) associating with each potential synthon in each stage of a combinatorial synthesis one or more tags uniquely identifying such synthon;

10           (b) linking to each compound synthesized from such synthon, or to a solid support upon which said compound is being synthesized, one or more tags uniquely identifying such synthon so that the reaction history of each compound in the resulting combinatorial chemistry library is defined by which  
15 tags are linked thereto;

(c) entering into a computerized system a representation of a compound; and

(d) displaying on an output device a representation of a set of one or more tags uniquely associated with said  
20 compound.

15. A method for planning the generation of combinatorial chemistry libraries without performing a chemical synthesis comprising:

25           (a) selecting criteria for a target library;

(b) entering said criteria into a computer-implemented system comprising a knowledge base containing rules for synthon selection;

5 (c) automatically generating a representation of a proposed library;

(d) evaluating said representation of a proposed library to determine the degree to which the members of said library meet the criteria selected in (a);

10 (e) updating said knowledge base as a function of said evaluating;

(f) repeating steps (c) through (e) until the target library members are fully identified.

15 16. The method of claim 15, wherein said knowledge base is initialized with rules obtained from interviewing scientists.

20 17. The method of claim 15, wherein said representation of a proposed library comprises representations of, for each stage in the combinatorial reaction series, the set of chemical structures of the contributions made, respectively, by each potential synthon in such reaction stage.

25 18. The method of claim 15, wherein said evaluating is performed by a scientist.

19. The method of claim 15, wherein said evaluating comprises:

- (i) enumerating said automatically generated representation of a proposed library to form a comprehensive representation of said proposed library;
- (ii) determining coefficients for said comprehensive representation of said proposed library; and
- (iii) comparing said coefficients for said comprehensive representation of said proposed library to said criteria for a target library.

20. The method of claim 19 wherein said enumerating is performed automatically.

21. The method of claim 20 wherein said determining coefficients for said comprehensive representation of said proposed library is performed automatically using computer-implemented compound evaluation algorithms.

22. The method of claim 21 wherein said comparing said coefficients for said comprehensive representation of said proposed library to said criteria for a target library is performed automatically.

23. The method of claim 19, wherein said determining coefficients for said comprehensive representation of said proposed library comprises:

5 (i) performing a statistical sampling of said comprehensive representation of said proposed library to form a representation of a subset of compounds in said proposed library; and

(ii) applying computer-implemented compound evaluation algorithms to said representation of a subset of  
10 compounds in said proposed library.

24. The method of claim 15, wherein said updating of said knowledge base as a function of said evaluating is performed automatically.

15

25. The method of claim 15, wherein said criteria for a target library comprises information on a target to be screened.

26. The method of claim 15, wherein said criteria relate  
20 to one or more of the following attributes: lipophilicity; hydrogen bonding ability; molecular weight; diversity of atom descriptors; potential for carcinogenicity; potential for toxicity.

25

27. An apparatus for representing a combinatorial chemistry library comprising:

5 (a) means for representing, for each stage in the combinatorial reaction series, the set of chemical structures of the contributions made, respectively, by each potential synthon in such reaction stage.

28. The apparatus of claim 27, further comprising means for representing that a contribution from a reaction stage can  
10 attach to a contribution from another reaction stage.

29. The apparatus of claim 28, further comprising means for representing that a contribution from any reaction stage can attach at any one or more positions to a contribution from any  
15 other reaction stage.

30. The apparatus of claim 27, further comprising means for identifying contributions made by each potential synthon in each reaction stage.

20

31. The apparatus of claim 30, wherein said means for representing comprises means for identifying one or more tags which uniquely identify one or more synthons making said contributions.



32. The apparatus of claim 31, wherein said means for representing comprises means for identifying said one or more synthons based on the identities of said one or more tags.

5           33. The apparatus of claim 31, wherein said means for identifying one or more tags comprises means for identifying distinguishable characteristics of said one or more tags.

10           34. The apparatus of claim 27, wherein said means for representing comprises means for indicating positions of attachment to contributions from other stages with labeled bonds.

15           35. The apparatus of claim 34, wherein said labeled bonds comprise numbered bonds.

20           36. The apparatus of claim 27 further comprising:  
            (b) means for enumerating said combinatorial library representation by attaching, at the indicated positions of attachment, a single member of the set of chemical structures for a reaction stage to a single member of the set of chemical structures for a different reaction stage, so as to represent the entire structure of one or more compounds in said combinatorial chemistry library.

37. The apparatus of claim 36 wherein means for enumerating said combinatorial library representation comprises means for omitting any and all unattached contributions from said comprehensive combinatorial library representation.

5

38. An apparatus for tracking the contents of small molecule combinatorial chemistry libraries comprising:

(a) means for entering into a computerized system a representation of a first set of one or more tags; and

10

(b) means for displaying on an output device a representation of a first compound identified by said first set of one or more tags.

15

39. The apparatus of claim 38 wherein said one or more tags comprise radio tags.

40. The apparatus of claim 38, wherein said one or more tags comprise tagging molecules.

20

41. An apparatus for tracking the contents of small molecule combinatorial chemistry libraries comprising:

(a) means for entering into a computerized system a representation of a compound; and

(b) means for displaying on an output device a representation of a set of one or more tags uniquely associated with said compound.

5           42. An apparatus for planning the generation of small molecule combinatorial chemistry libraries comprising:

(a) means for entering criteria for a target library into a computer-implemented system comprising a knowledge base containing rules for synthon selection;

10           (b) means for automatically generating a representation of a proposed library;

(c) means for evaluating said representation of a proposed library to determine the degree to which the members of said library meet the criteria entered in (a);

15           (d) means for updating said knowledge base as a function of said evaluating.

          43. The apparatus of claim 42, wherein said knowledge base is initialized with rules obtained from interviewing  
20 scientists.

          44. The apparatus of claim 42, wherein said representation of a proposed library comprises representations of, for each stage in the combinatorial reaction series, the set of

chemical structures of the contributions made, respectively, by each potential synthon in such reaction stage.

45. The apparatus of claim 42, wherein said means for  
5 evaluating comprises:

(i) means for enumerating said automatically generated representation of a proposed library to form a comprehensive representation of said proposed library;

(ii) means for determining coefficients for said  
10 comprehensive representation of said proposed library; and

(iii) means for comparing said coefficients for said comprehensive representation of said proposed library to said criteria for a target library.

46. The apparatus of claim 45, wherein said means for  
15 determining coefficients for said comprehensive representation of said proposed library comprises:

(i) means for performing a statistical sampling of said comprehensive representation of said proposed library to  
20 form a representation of a subset of compounds in said proposed library; and

(ii) means for applying computer-implemented compound evaluation algorithms to said representation of a subset of compounds in said proposed library.

25

47. The apparatus of claim 42, wherein said criteria for a target library comprises information on a target to be screened.

48. The apparatus of claim 42, wherein said criteria  
5 relate to one or more of the following attributes: lipophilicity; hydrogen bonding ability; molecular weight; diversity of atom descriptors; potential for carcinogenicity; potential for toxicity.

49. A method for identifying suitable synthons for  
10 generation of a target combinatorial chemistry library meeting desired criteria, without performing a chemical synthesis, comprising:

- (a) selecting criteria for a target library;
- (b) entering said criteria into a computer-  
15 implemented system comprising a knowledge base containing rules for synthon selection;
- (c) automatically generating a representation of a proposed library to determine the degree to which the members of said library meet the criteria selected in (a);
- 20 (d) evaluating said representation of a proposed library;
- (e) updating said knowledge base as a function of said evaluating;
- (f) repeating steps (c) through (e) until the  
25 target library members are fully identified; and

(g) identifying as suitable synthons those which cause the generation of said fully identified target library members.

5           50. A method of representing a combinatorial library comprising the steps of:

(a) representing, for each stage in the combinatorial reaction series, the set of chemical structures of the contributions made, respectively, by each potential synthon in  
10 such reaction stage;

a first subset of contributions from a reaction stage, which first subset of contributions is not to be combined with a contribution from a previous or subsequent reaction stage, being represented separately from a second subset of contributions  
15 from the same reaction stage, which second subset of contributions is to be combined with such contribution from the previous or subsequent reaction stage; and

(b) representing, for each such subset, the contributions from other reaction stages with which it will be  
20 combined.

51. An apparatus for representing a combinatorial chemistry library comprising:

(a) means for representing, for each stage in the combinatorial reaction series, the set of chemical structures of  
25

the contributions made, respectively, by each potential synthon in such reaction stage;

the contributions from at least one reaction stage being divided into subsets, wherein at least one of the subsets is not to be combined with a contribution from a previous or subsequent reaction stage; and

(b) means for associating each such subset with the contributions from other reaction stages with which such subset will be combined.

10

52. The apparatus of claim 51 further comprising means for entering a representation of said association into a computer.

53. The method of claim 50 or 58 further comprising associating with each contribution a tag uniquely identifying such contribution, such that a compound containing such contribution in the resulting combinatorial chemistry library may be identified by reference to such tag.

20

54. The apparatus of claim 53A further including means for determining in a computer, for a subset of contributions in a reaction stage, which contributions from other reaction stages are combined with the members of such subset, by reference to the tags associated with members of the combinatorial library.

25

55. A method of identifying chemical compounds produced by the reaction of a plurality of synthons utilizing selective combination combinatorial chemistry techniques, said method comprising the steps of:

5 associating a tag with each synthon, said tag representing a tagging molecule identifying the contribution made by said synthon;

inputting into a computer the tags associated with a compound to be identified;

10 determining, by reference to such tags, the identities of all contributions in the compound.

56. A method of determining the reaction steps to synthesize a compound of interest utilizing combinatorial chemistry with selective combination, said method comprising the steps of:

15 (a) storing in a computer, for each member of a combinatorial library including the compound of interest, information sufficient to represent tags associated with each synthon utilized in the synthesis of said member;

20 (b) associating, with the information representing each tag, information about a reaction step utilizing said synthon in the synthesis of said library;

(c) retrieving the information stored and associated in steps (a) and (b) with respect to the compound of interest; and

25



(d) determining, from said information, the reaction steps used to synthesize the compound of interest.

57. A method of representing a reaction series utilized  
5 in combinatorial chemistry with selective combination, said method comprising the steps of:

(a) storing, in a computer, information indicative of (i) a plurality of reaction stages, (ii) one or more subsets of synthons or products into which each reaction stage is divided, at  
10 least one of such reaction stages being divided into a plurality of such subsets, and (iii) information indicating which subset will be combined with a contribution from a previous or subsequent reaction stage;

(b) inputting, into said computer, representations  
15 of tags associated with a compound synthesized by said reaction series;

(c) generating, from said input representation, a representation of different reactions in said reaction series.

20 58. A method of synthesizing a combinatorial library of compounds, comprising the steps of:

dividing the synthons to be reacted into a plurality of groups according to reaction stage;

further dividing synthons in a particular reaction  
25 stage or the products of a reaction stage into a plurality of

subsets, wherein the respective members of each subset correspond to contributions to such combinatorial library;

wherein at least one of the subsets is not to be combined with a contribution from a previous or subsequent reaction stage.

59. The method of claim 58 wherein the products of a reaction stage are divided into aliquots, each aliquot having substantially the same composition, and wherein each aliquot is reacted with a different subset from a subsequent reaction stage.

60. The method of claim 58 wherein products of a reaction stage are divided into aliquots, each aliquot having substantially the same composition, and wherein each aliquot is reacted with a different synthon from a subsequent reaction stage.

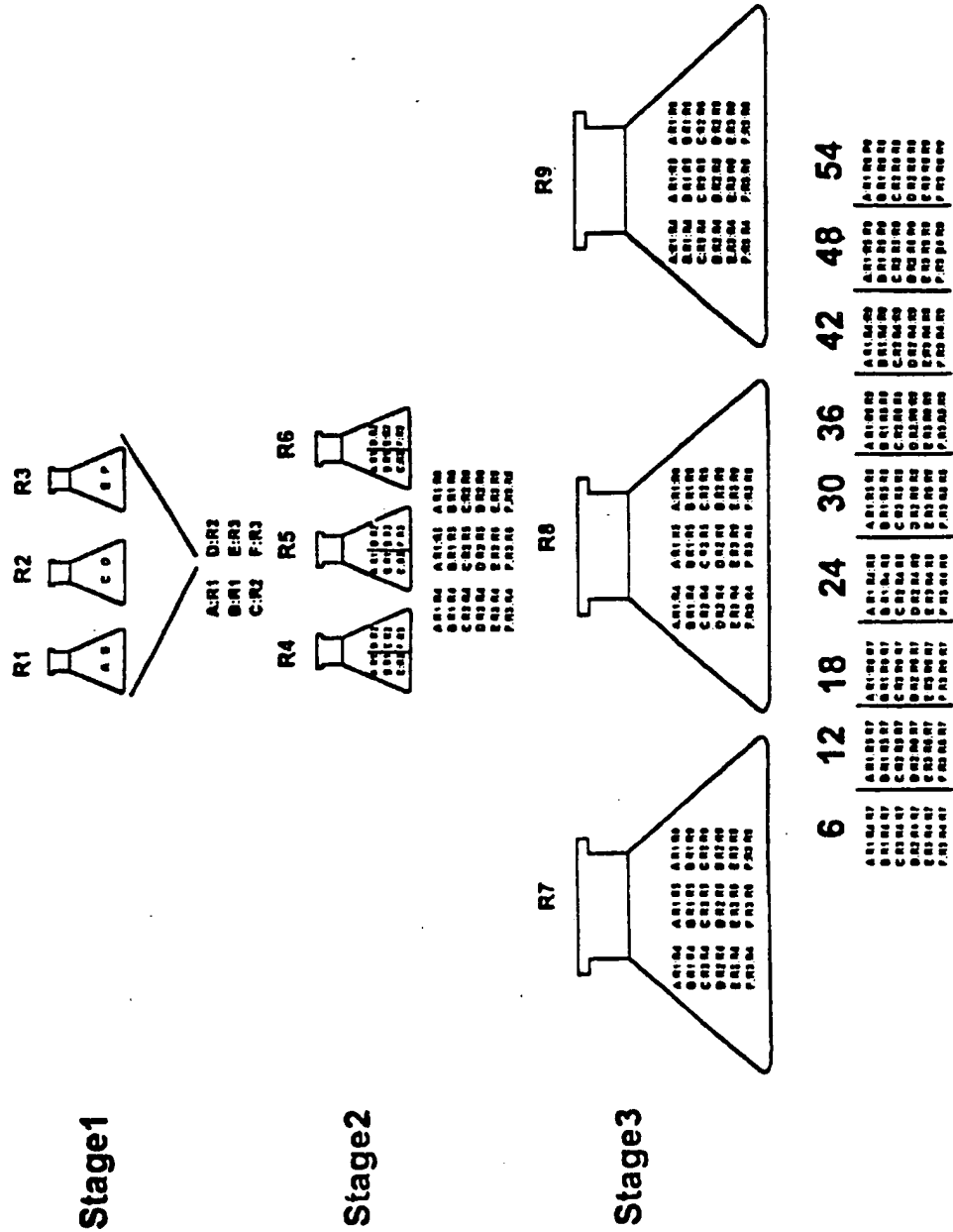
61. The apparatus of claim 51 further comprising means for associating with each contribution a tag uniquely identifying such contribution, and means for identifying a compound containing such contribution in the combinatorial library by reference to such tag.

62. The method of claim 59 wherein at least two aliquots into which a reaction stage is divided contain different portions of said products.

63. The method claim 60 wherein at least two aliquots into which a reaction stage is divided contain different portions of said products.

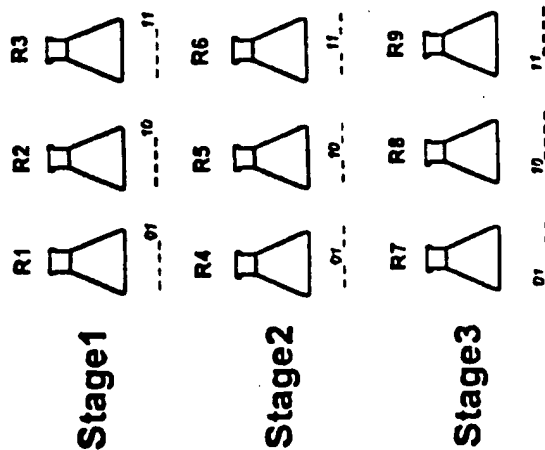
1/15

**FIG. 1**

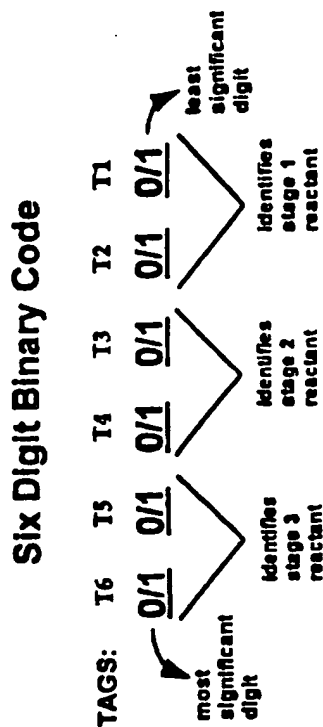


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**FIG. 2A**



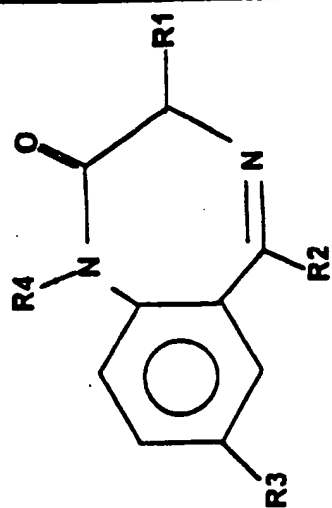
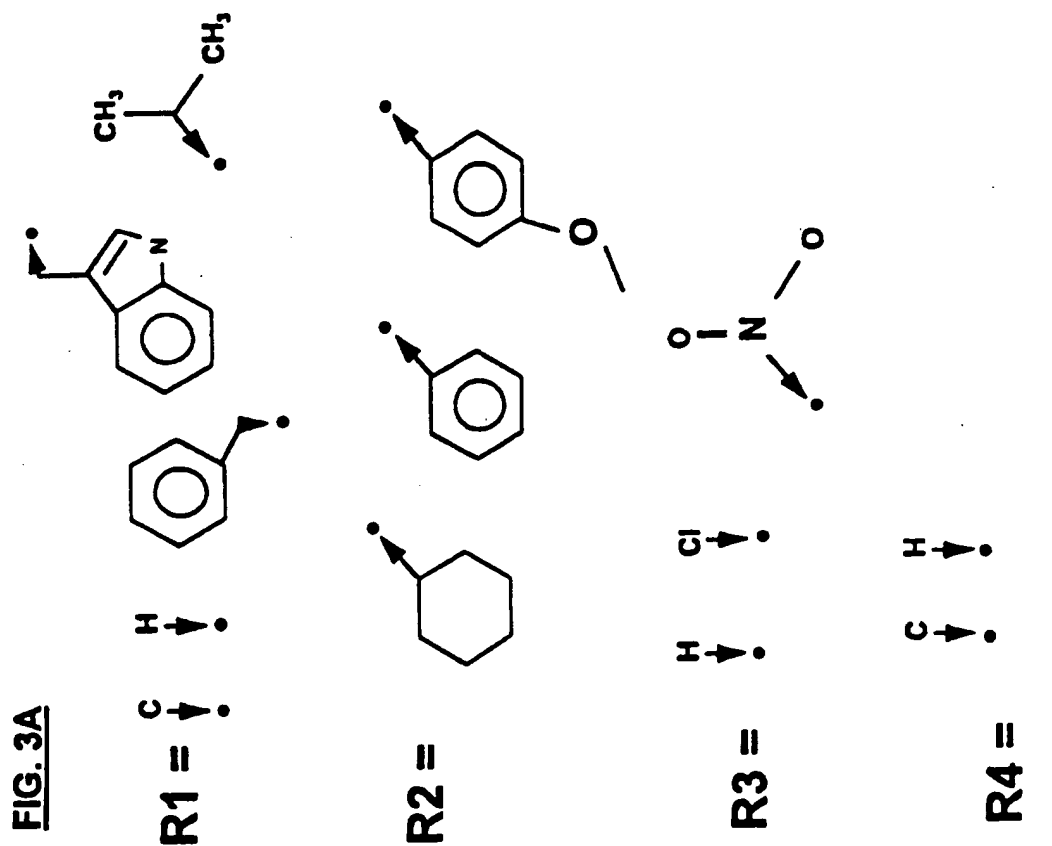
**FIG. 2B**



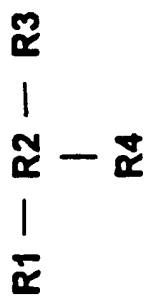
**FIG. 2C**

	reaction history	binary code	base on solid support
Compound A:	R3:R5:R9	= 111011	= T1 T2 T4 T5 T6
Compound B:	R1:R6:R8	= 101101	= T1 T3 T4 T6
Compound C:	R2:R4:R7	= 010110	= T2 T3 T5

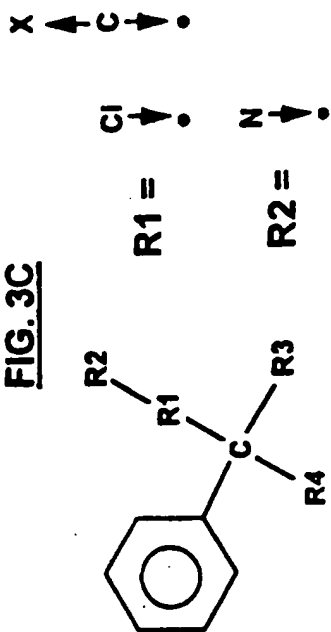
3/15



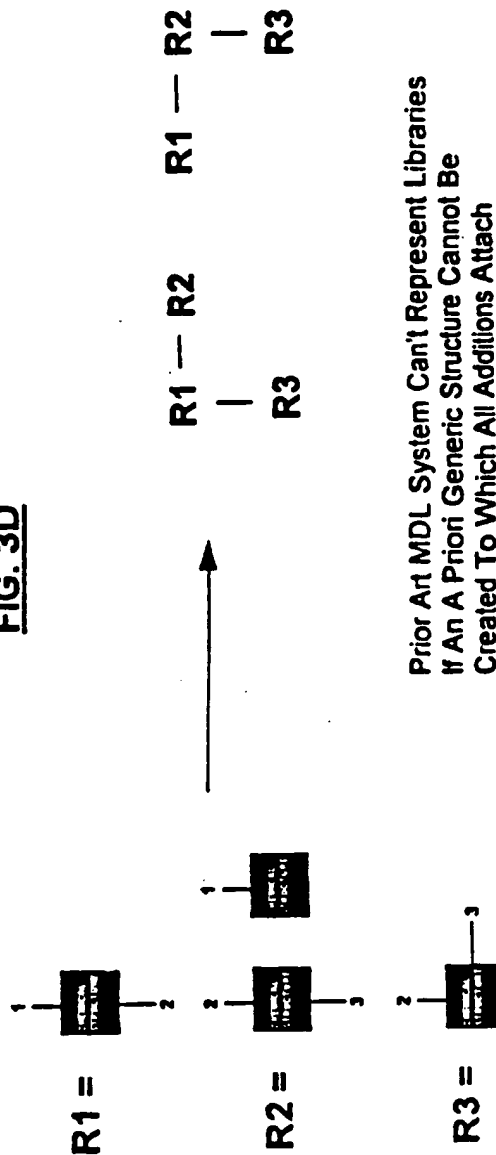
4/15

**FIG. 3B**

Core Structure Which Cannot  
Be Represented by Prior Art MDL  
System

**FIG. 3C**

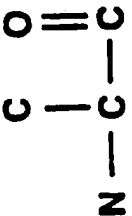
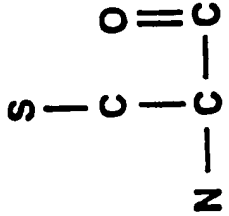
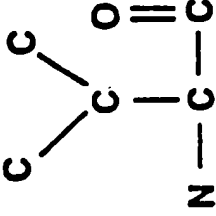
Prior Art MDL System Can't Represent Additions  
Which Attach Only In A Subset Of Structures Formed  
In Previous Stages

**FIG. 3D**

Prior Art MDL System Can't Represent Libraries  
If An A Priori Generic Structure Cannot Be  
Created To Which All Additions Attach

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**FIG. 4A**

MONOMER STRUCTURE	DAYLIGHT LINEAR REPRESENTATION	USER-ASSIGNED NAME
	<chem>NC(C)C(=O)</chem>	Ala
	<chem>NC(CS1)C(=O)</chem>	Cys
	<chem>NC(C(C)C)C(=O)</chem>	Val



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**FIG. 4B**

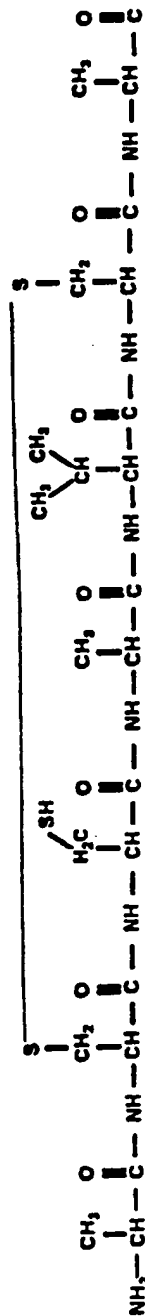
**Polymerized  
Molecule = Ala-Cys1-Cys-Ala-Val-Cys1-Ala  
Represented as  
Linked Monomer  
Names**

**Daylight Linear Representation**

**=**

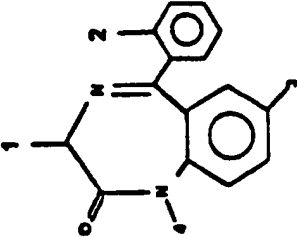
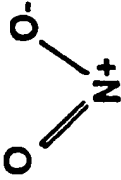
**NC(C)C(=O)-NC(CS1)C(=O)-NC(CS)C(=O)-NC(C)C(=O)-NC(C(C)C)C(=O)-NC(CS1)C(=O)-NC(C)C(=O)**

**Chemical Structure Represented:**



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**FIG. 4C**

MONOMER STRUCTURE	DAYLIGHT LINEAR REPRESENTATION	USER-ASSIGNED NAME
	<chem>C1 N=C(c1ccccc1)c2cc3ccc(N4C7=O</chem>	Pam
[H]	[H]	Hx
C	C	Mex
Br1	Br1	Brx
	<chem>O=[N+][O-]</chem>	Nitrox

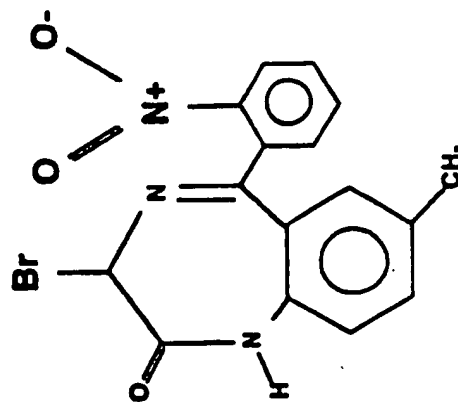
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**FIG. 4D**

Contents of  
Combinatorial  
Library = Pam2768.[Brx;Clx;Fx;Hx;Ix]2.  
[Clx;Fx;Hx;Nitrox]7.[Eohx;Etx;  
Hx;McpX;Mex;Mohx;Phex;Ppox;  
Tfex;Tppx]6.[Carx;Hx;Ohx]8

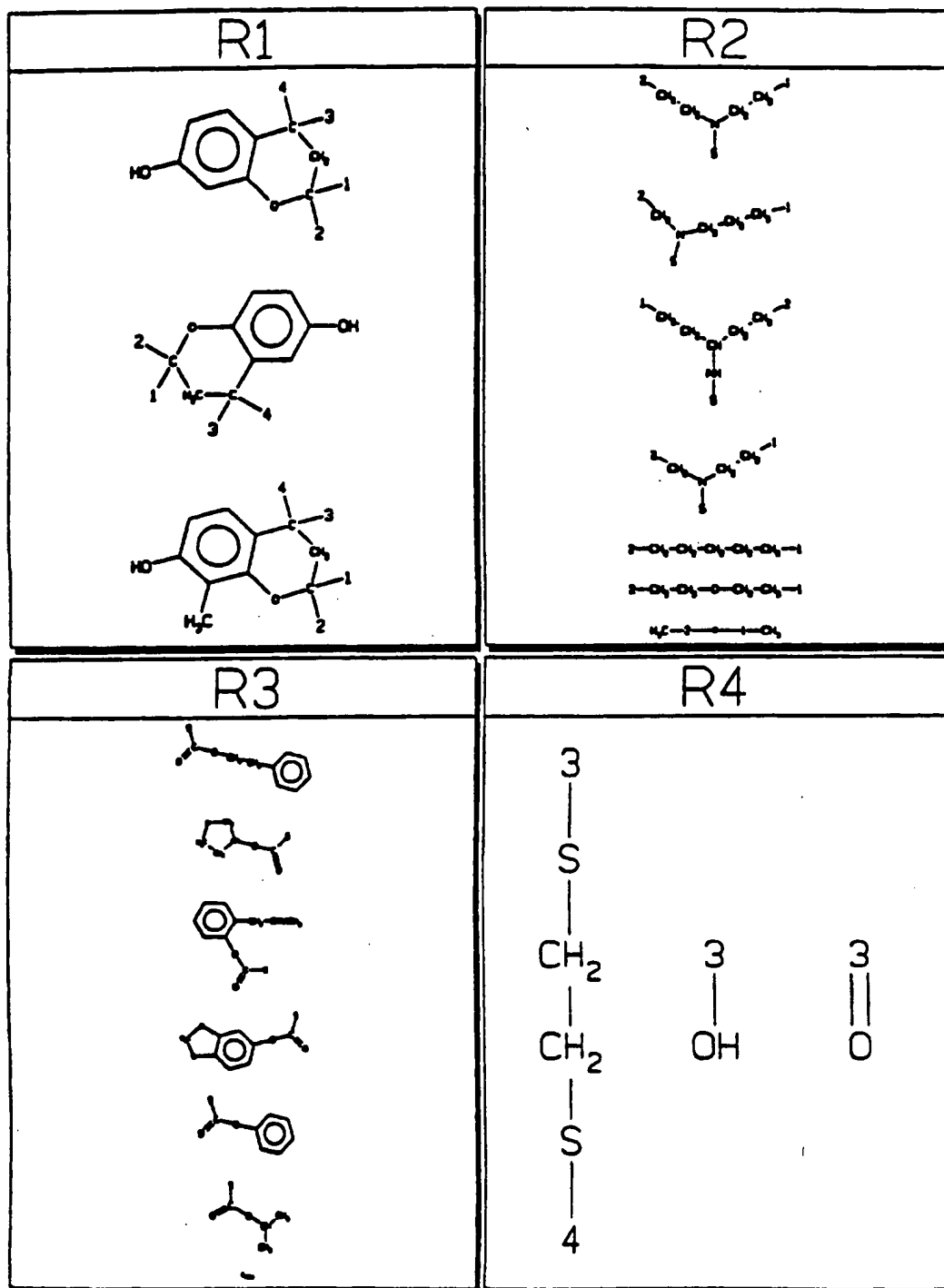
**FIG. 4E**

Pam2768.BrX2.Nitrox7.Mex6.Hx8 =

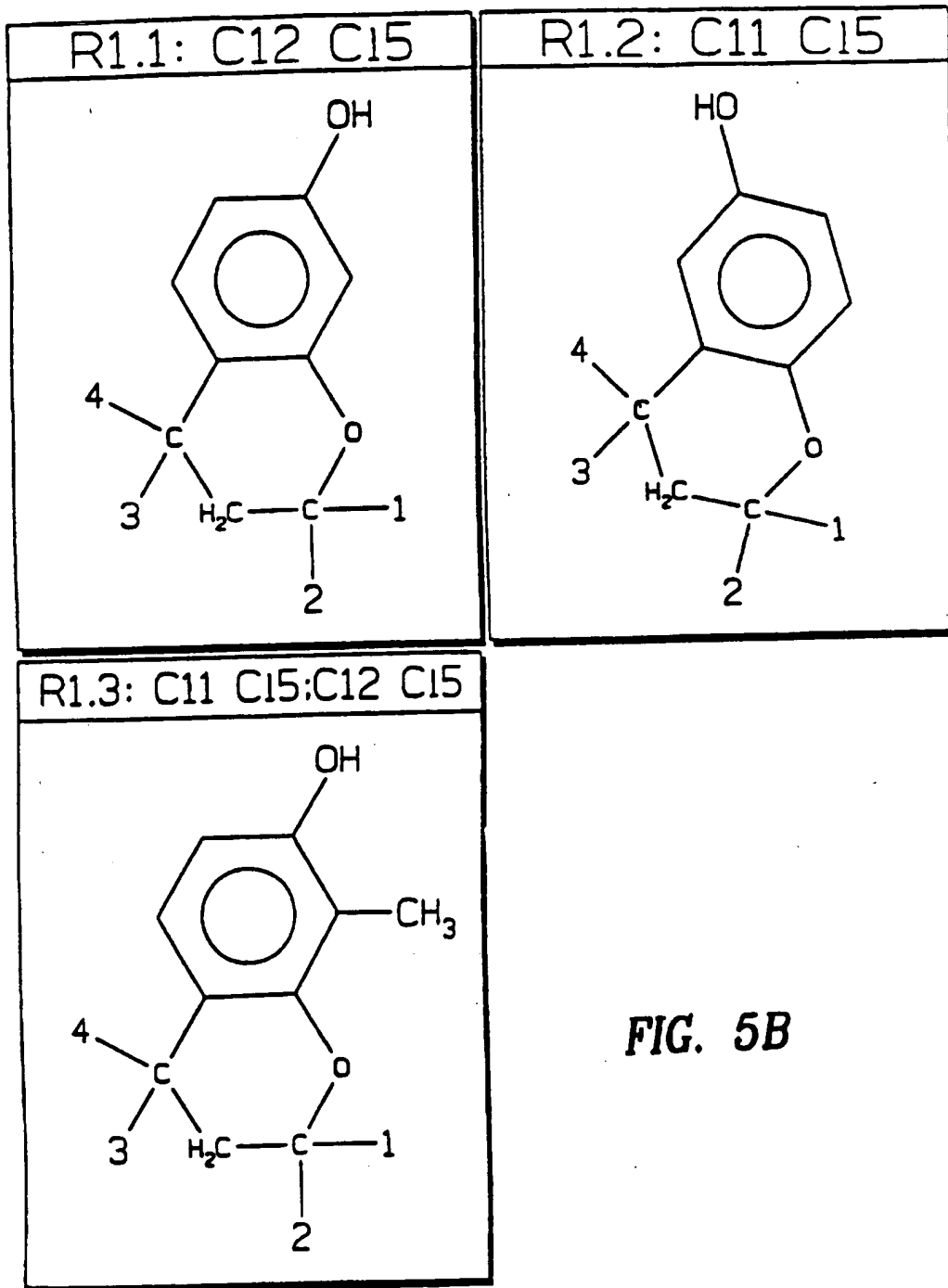


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FIG. 5A



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**FIG. 5B**

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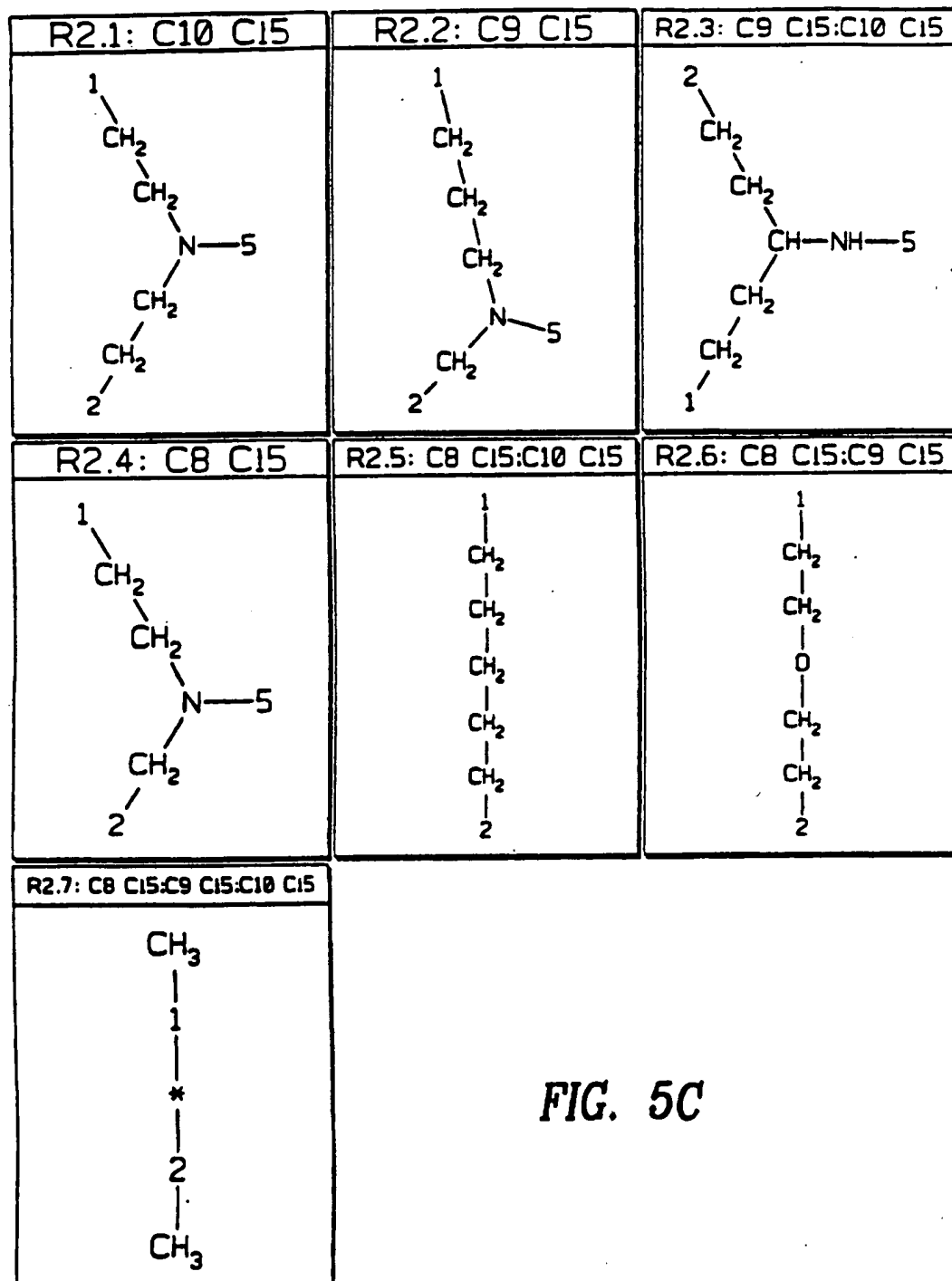


FIG. 5C

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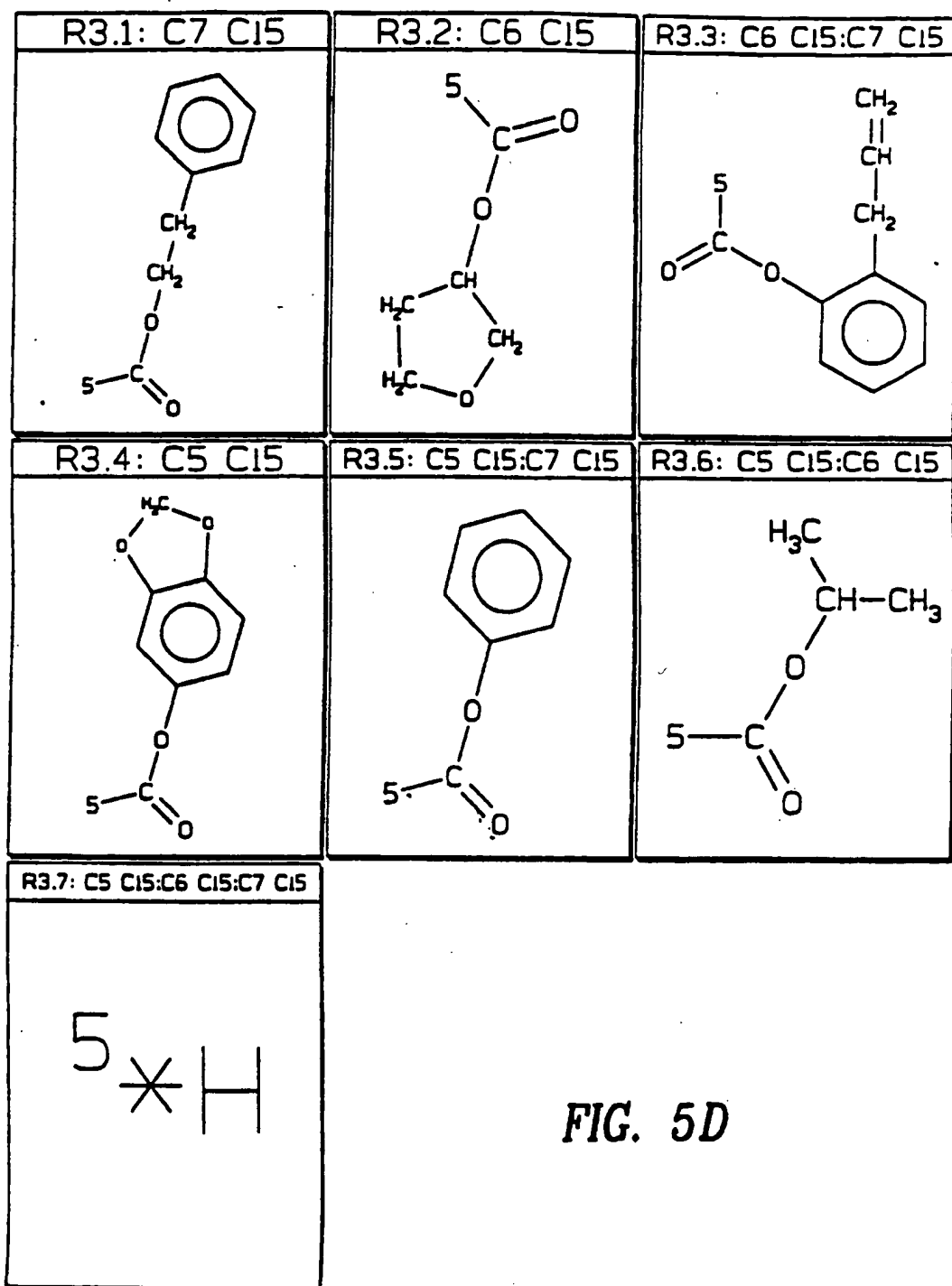
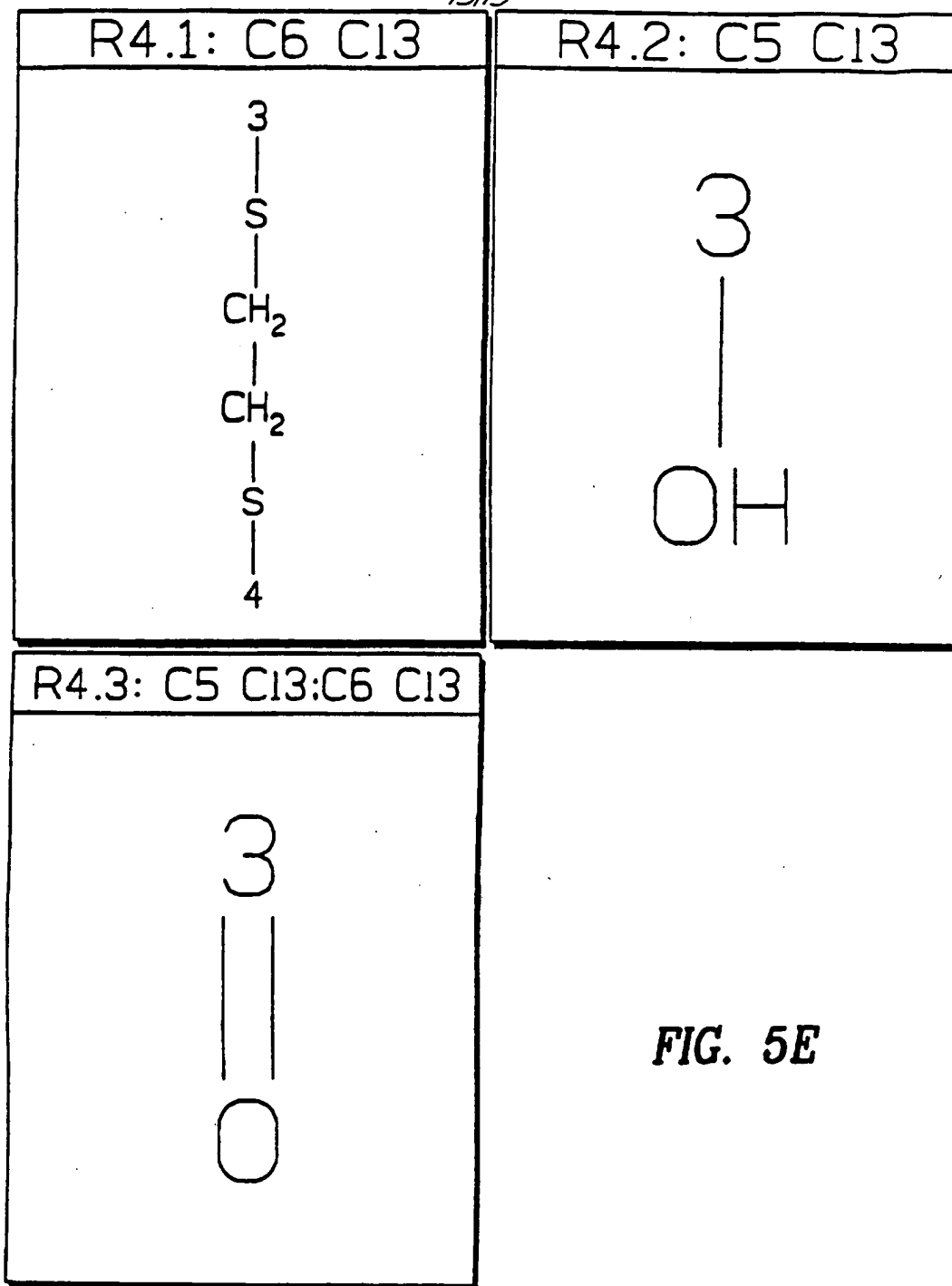


FIG. 5D

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**FIG. 5E**



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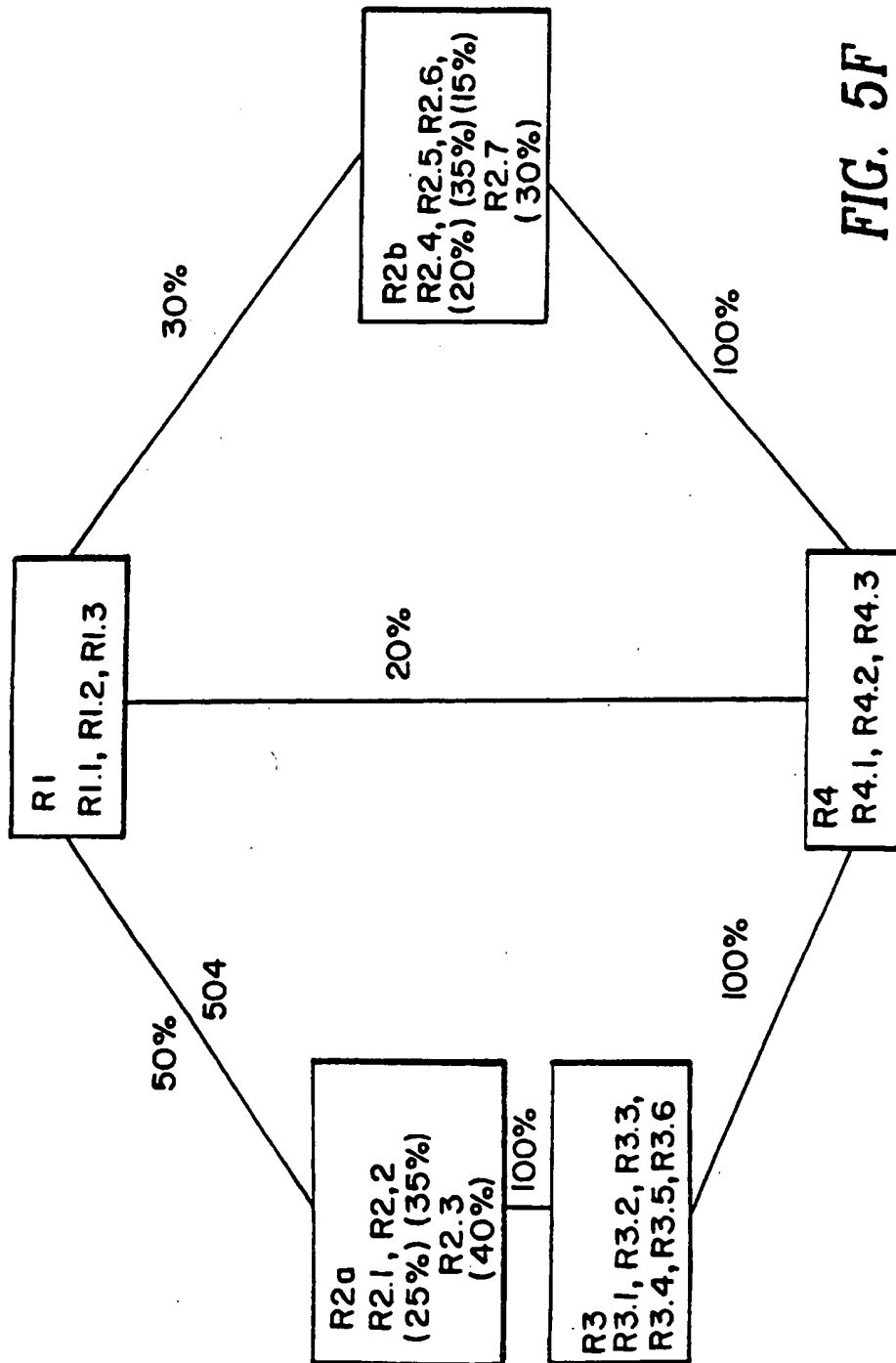
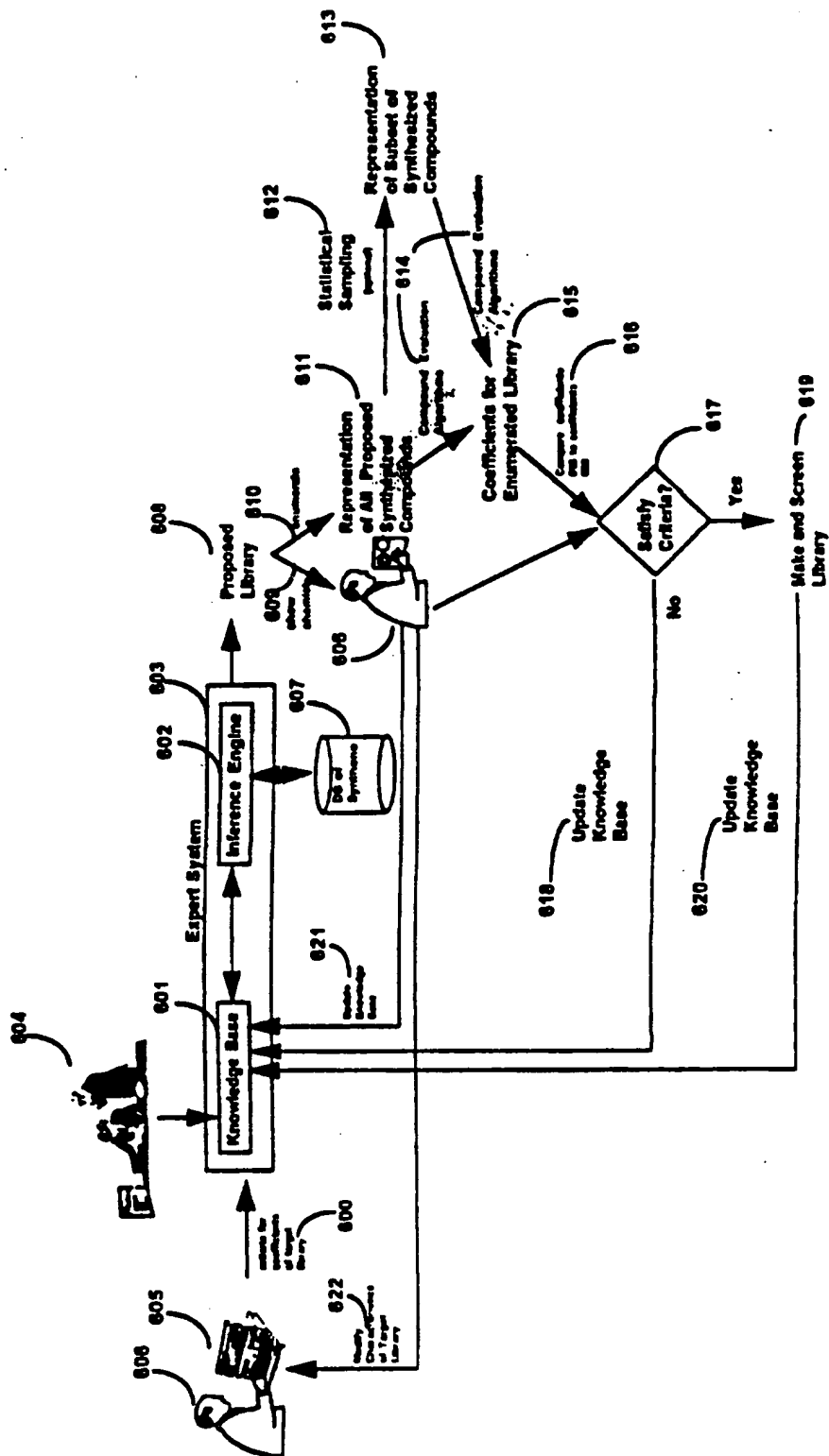


FIG. 5F

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**FIG. 6**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/02176

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12Q 1/68; G01N 33/53, 543

US CL : 364/496-499; 435/6, 7.1; 436/501, 518

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 364/496-499; 435/6, 7.1; 436/501, 518

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog, Aps

search terms: combinatorial chemical library, tag, synthon, reaction history

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,565,324 A (STILL et al) 15 October 1996, abstract, col. 1, lines 15 - col. 3, line 45, col. 5, line 35 - col. 8, line 15	1-63
A,P	US, 5,573,905 A (LERNER et al.) 12 November 1996, abstract, col. 2, line 44 - col. 3, line 59, col. 8, line 54 - col. 15, line 49	1-63
A,P	BALDWIN ET AL., "Design, Synthesis, and Preparation of an Encoded Small-Molecule Library for a Wide Variety of 96-Well Based Bioassays" Methods in Molecular and Cellular Biology, 1996 vol. 6, no. 1, pages 74-88 especially pages 74-80	1-63

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"I" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 MAY 1997

Date of mailing of the international search report

24 JUN 1997

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/02176

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Ohlmeyer et al., "Complex Synthetic Chemical Libraries Indexed with Molecular Tags", Proc. of the National Academy of Sciences of the United States of America, 1993 vol. 90, n. 23, pages 10922-10926, especially pages 10922-10924	1-63
A	Brenner et al., "Encoded Combinatorial Chemistry" Proc. Natl. Acad. Sci. U.S.A., 1992 vol. 89, n.12. pages 5381-5383 especially pages 5381-5383	1-63